Journal of Forensic and Legal Medicine 20 (2013) 1122–1125

Contents lists available at ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Original communication

# Toxicology, circumstances and pathology of deaths from acute alcohol toxicity

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ARTICLE INFO

*Article history:*
Received 18 March 2013
Received in revised form
2 September 2013
Accepted 7 September 2013
Available online 18 September 2013

*Keywords:*
Alcohol
Mortality
Toxicity
Toxicology
Demographics
Disease

ABSTRACT

Alcohol consumption makes a large contribution to premature mortality. In order to extend our understanding of the characteristics, circumstances, toxicology and pathology of alcohol toxicity deaths, all cases presenting to the Department of Forensic Medicine Sydney between 1/1/1997–31/12/2011 with blood alcohol concentrations (BACs) ≥0.300 g/100 ml and where the direct cause of death was acute alcohol toxicity were retrieved ($n = 83$). The mean age was 47.2 yrs and 77.1% were male. The majority (81.9%) of deaths occurred in a home environment, and did not vary across month or day of the week. In 91.6% of cases, a history of alcoholism or heavy alcohol consumption was reported. None were in any form of substance dependence treatment at the time of death. The mean BAC was 0.420 g/100 ml (range 0.300–0.741 g/100 ml). In 33.7% of cases, other substances were detected, predominantly diazepam (28.9%). BACs did not vary significantly by gender, age or BMI. Urine/BAC ratios of >1.25 were seen in 6/43 cases where both samples were available. Cardiac disease was noted in 75.9% of cases and hepatic disease in 91.6%. The only alcohol-related organic brain syndrome pathology identified at autopsy was vermal cerebellar degeneration.



## 1. Introduction

Alcohol consumption makes a large contribution to premature mortality, through a range of causes, including alcohol-related disease, accidents, homicide and suicide.[1–5] This impact is considerable, with national increases of 1 L per capita alcohol consumption having been associated with a 1% increase in all-cause mortality.[4]

One of the major causes of alcohol-related death is acute alcohol toxicity. Alcohol in high blood alcohol concentrations (BACs) induces respiratory depression, and death due to acute alcohol toxicity is the predominant form of mono-substance toxicity death.[1,3,6–10] At BACs ≥0.300 g/100 ml there is respiratory depression, as well as marked impairment of perceptual, cognitive and motor functions, however the minimum fatal concentration is generally been considered to be > 0.400 g/100 ml.[2,3,11–16] Fatal concentrations will, however vary markedly with the tolerance of the individual. Alcohol dependence is also associated with high levels of systemic disease, that may increase physical stress and increase the likelihood of death.[1,3,17–20] Survival has been reported in cases with BACs in excess of 1.00 g/100 ml, and death where the BAC was less than 0.300 g/100 ml.[3,11–16,21,22]

In earlier work[23] we reported on all cases of sudden or unnatural deaths presenting to the Department of Forensic Medicine (DOFM) in Sydney with a BAC ≥0.300 g/100 ml that occurred between 1 January 1997 and 31 December 2011. The current study specifically examined fatal cases of acute alcohol toxicity. We aimed to extend our knowledge of fatal acute alcohol toxicity by providing a comprehensive examination of the characteristics of cases (e.g. marital status, alcohol problem history), quantitative toxicology, the circumstances in which death occurred (location, type of beverage involved), and the prevalence of pre-existing systemic disease. Specifically, the study aimed to:

1. Determine the characteristics and toxicology of fatal cases of acute alcohol toxicity with a BAC ≥0.300 g/100 ml;

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http://dx.doi.org/10.1016/j.jflm.2013.09.002

2. Determine circumstances of death of fatal cases of acute alcohol toxicity; and
3. Determine the levels of systemic disease of fatal cases of acute alcohol toxicity.

## 2. Methods

### 2.1. Case identification

Autopsy reports and police investigative summaries of all cases in which BACs were ≥0.300 g/100 ml and who underwent medicolegal autopsy at the DOFM in Sydney between 1 January 1997 and 31 December 2011 were retrieved. The current study examined those cases with BACs ≥0.300 g/100 ml where the direct cause of death was deemed solely due to acute alcohol toxicity by the autopsy pathologist. Cases where death was directly attributed to chronic alcoholism, multiple drug toxicity or other causes of death (e.g. accidents) were excluded from this study.

The DOFM is located in central Sydney, and is the primary forensic pathology centre in New South Wales (NSW), conducting between 2000 and 2500 autopsies per year. Permission to inspect the files was received from the Sydney Local Health District human research ethics committee. All cases were reviewed by the authors.

In NSW a case must be reported to the Coroner where a person dies a violent or unnatural death. The majority of such cases undergo a standardised forensic autopsy, with examination of all major organs and quantitative toxicological analysis. Cause of death is determined by the forensic pathologist on the basis of circumstances of death, the autopsy findings and the toxicological analyses. Circumstances of death, and case histories, were obtained from accompanying police reports to the Coroner.

All autopsy blood samples were taken peripherally (femoral or subclavian vessels). Toxicological data were reported for alcohol, cannabis (determined by the presence of Δ-9-THC), opioids, psychostimulants, benzodiazepines, antidepressants and antipsychotic medications. In cases where there was prolonged hospitalisation prior to death, antemortem toxicology taken at admission was reported, and drugs administered by hospital and medical staff excluded. All samples were screened by immunoassay and either by gas chromatography or high-performance liquid chromatography (HPLC) for drugs of abuse and common therapeutic substances. Urine and vitreous humor alcohol concentrations were reported where these analyses were conducted. A urine/blood ratio of greater than 1.25 is generally viewed as indicative of the person as having reached the post-absorptive phase.[13,24,25] All analyses were conducted by the Forensic Toxicology Laboratory of the NSW Forensic & Analytical Science Service (formerly the Division of Analytical Laboratories).

### 2.2. Statistical analyses

Where distributions were highly skewed, median values and ranges were reported, otherwise mean values and standard deviations (SD) were presented. For bivariate comparisons, *t*-tests or chi square were used. Pearson product moment correlations were used to examine correlations between continuous variables. All analyses were conducted using IBM SPSS Statistics 20.0.[26]

## 3. Results

### 3.1. Demographic and physical characteristics

A total of 263 cases were identified with a BAC ≥0.300 g/100 ml, of which 83 (31.6%) had death attributed to acute alcohol toxicity. This sub-group of 83 cases constituted our study population. The mean age of decedents was 47.2 yrs (SD 12.3, range 22–83 yrs) and 77.1% were male. A minority (20.5%) were married or in a domestic relationship, and 25.3% were in paid employment. The mean BMI was 27.0 kg/m$^2$ (SD 5.4, range 16.7–50.0 kg/m$^2$). A single case (1.2%) was underweight, 30.1% were overweight and 22.9% were obese.

### 3.2. Circumstances of death

The majority of deaths (81.9%) occurred in a home environment. Other locations were: park (4.8%), hotel (2.5%), railway station (2.4%), car (2.4%), hospital (2.4%) and public toilet (1.2%). Cases did not significant vary across month ($p = .64$) or day of the week ($p = .17$).

In 91.6% of cases, a history of alcoholism or heavy alcohol consumption was reported, with no gender difference (males 89.1%, females 100%, $p = .13$). In a single case death followed a drinking contest. None were in any form of substance dependence treatment at the time of death. In 5 cases (6.0%) the decedent had undergone detoxification in the two weeks prior to death. No case was a suicide.

**Table 1**
Major autopsy findings of fatal cases of acute alcohol toxicity.

| Pathology | Males ($n = 64$) % | Females ($n = 19$)% | All cases ($n = 83$)% | Comparisons |
|---|---|---|---|---|
| *Cardiac* | 79.7 | 62.3 | 75.9 | $\chi^2 = 2.2$, $p = .14$ |
| Cardiomegaly | 26.6 | 15.8 | 24.1 | |
| Left ventricular hypertrophy | 14.1 | 15.8 | 14.5 | |
| Ventricle dilation | 18.8 | 5.3 | 15.7 | |
| Cardiomyopathy | 17.2 | 5.3 | 14.5 | |
| Fibrosis | | | | |
| Myocardial fibrosis | 20.3 | 31.6 | 22.9 | |
| Interstitial fibrosis | 31.2 | 15.8 | 27.7 | |
| Perivascular fibrosis | 23.4 | 26.3 | 24.1 | |
| Severe atherosclerotic occlusion (>75%) | 14.1 | 5.3 | 12.0 | |
| *Hepatic* | 89.1 | 100 | 91.6 | $\chi^2 = 2.3$, $p = .13$ |
| Cirrhosis | 23.4 | 22.1 | 22.9 | |
| Fibrosis (excluding cirrhosis) | 14.1 | 33.6 | 18.1 | |
| Steatosis | | | | |
| Severe | 35.9 | 42.1 | 37.3 | |
| Moderate | 21.9 | 36.8 | 25.3 | |
| Mild | 17.2 | 21.1 | 18.1 | |
| Hepatomegaly | 22.6 | 15.8 | 21.0 | |
| *Pulmonary* | 29.7 | 21.2 | 27.7 | $\chi^2 = 0.5$, $p = .46$ |
| Emphysema | 9.4 | 5.3 | 8.4 | |
| Asthma | 9.4 | 5.3 | 8.4 | |
| Bronchopneumonia | 6.2 | 0 | 4.8 | |
| Bronchitis | 3.1 | 0 | 2.4 | |
| Pleural fibrous adhesions | 7.8 | 5.3 | 7.2 | |
| Sarcoidosis | 0.0 | 10.5 | 2.4 | |
| *Renal* | 32.8 | 36.8 | 33.7 | $\chi^2 = 0.1$, $p = .74$ |
| Nephrosclerosis | 26.6 | 36.8 | 28.9 | |
| Fibrosis | 14.1 | 0 | 10.8 | |
| Cysts | 4.7 | 5.3 | 4.8 | |
| *Pancreatic* | | | | |
| Chronic pancreatitis | 20.0 | 10.5 | 18.1 | $\chi^2 = 0.9$, $p = .33$ |
| *Neurologic*[a] | 17.2 | 5.6 | 14.6 | $\chi^2 = 1.5$, $p = .22$ |
| Alcohol-related cerebellar degeneration | 14.1 | 5.6 | 12.2 | |
| Alcohol-related hippocampal atrophy | 3.2 | 0 | 2.4 | |
| Alcohol-related cortical atrophy | 1.6 | 0 | 2.4 | |

[a] $n = 82$. One female case not examined.

The type of alcohol consumed prior to death was described in the police investigation in 48 cases. Spirits were reported in 28 of these cases, so-called "methylated spirits" (denatured alcohol) in 11, wine in 9 and beer in 6.

### 3.3. Toxicology

The mean BAC was 0.416 g/100 ml (SD 0.080, range 0.300–0.741 g/100 ml). At the lower end of the distribution, 19.3% had BACs between 0.300 and 0.349 g/100 ml. BACs in excess of 0.50 g/100 ml were seen in 14.5% of cases. There were no differences between males and female BACs ( 0.416 vs. 0.415 g/100 ml, $t_{81} = 0.06$, $p = .96$). Neither age ($r = 0.03$, $p = .80$) nor BMI ($r = -0.21$, $p = .06$) were significantly correlated with BAC.

In 43 cases urine samples were also analysed, with a mean alcohol concentration of 0.485 g/100 ml (SD 0.111, range 0.243–0.793 g/100 ml). There were no differences between males and females urine concentrations (0.479 vs. 0.525 g/100 ml, $t_{41} = 0.94$, $p = .35$). In 34/43 of these cases, urine alcohol concentrations exceeded BAC and, overall, were 1.11 times higher than mean BAC (0.485 vs. 0.437 g/100 ml, $t_{42} = 4.3$, $p < .001$). Urine/BAC ratios in excess of 1.25 were seen in 6/43 cases.

In 30 cases, analyses of vitreous humour were conducted, with a mean alcohol concentration of 0.453 g/100 ml (SD 0.088, range 0.314–0.715 g/100 ml), with no difference between males and females concentrations (0.430 vs. 0.452 g/100 ml, $t_{29} = 0.48$, $p = .63$). In 29/30 of these cases, vitreous humour concentrations exceeded BAC and, overall, were 1.15 times higher than mean BAC (0.453 vs. 0.393 g/100 ml, $t_{29} = 6.0$, $p < .001$). Vitreous humour/BAC ratios in excess of 1.25 were seen in 6/30 cases.

In 33.7% of cases other substances were detected, predominantly diazepam (28.9%). Antidepressants were present in 6 cases (7.2%) and olanzapine in two. Morphine (0.05 mg/L) was detected in a single case, and Δ-9-THC in a single case. No other psychotropic substances were detected. There was no significant difference between the mean BACs of alcohol only cases and those in which other substances were present (0.421 vs. 0.406 g/100 ml, $p = .45$).

### 3.4. Major autopsy findings

Six cases tested positive for hepatitis C, while no cases were HIV positive. Ketoacidosis was diagnosed in three males. The mean heart weight was 435.5 g (SD 99.4, range 200–694 g). Cardiac disease was noted in 75.9% of cases (males 79.7%, females 63.2%, $p = .14$), most commonly cardiomegaly (Table 1). Ischaemic heart disease (indicated by severe atherosclerotic occlusion and/or myocardial scarring) was diagnosed in 31.3%.

The mean liver weight was 1966.8 g (SD 579.8, range 980–3900 g). Hepatic disease was present in 91.6% of cases (males 89.1%, females 100%, $p = .13$), most commonly severe steatosis. Chronic pancreatitis was noted in a fifth of cases, and did not significantly differ by gender ($p = .33$). Pulmonary disease was diagnosed in 27.7% of cases (males 29.7%, females 21.1%, $p = .46$), with chronic lung disease (emphysema, asthma) present in 16.8%. Aspiration of vomitus was noted in 7 cases (8.4%).

Renal disease was present in 33.7% of cases (males 32.8%, females 36.8%, $p = .74$), most frequently nephrosclerosis (24 cases). Alcohol-related neurologic pathology was present in 14.6% of cases, with no gender difference (males 17.2%, females 5.6%, $p = .22$). The most common neurologic presentation was vermal cerebellar degeneration. There were no cases of Wernicke's encephalopathy or other forms of organic brain syndrome.

## 4. Discussion

The current study provided novel data from a large case series on of the demographic, toxicological and pathological characteristics of cases of alcohol toxicity, as well as the circumstances in which death occurred. Consistent with earlier reports,[11–16] the typical profile in this series was a single, middle-aged male, not in paid employment, with a long history of heavy drinking. More broadly, this profile is similar to the characteristics of cases of toxicity death from other drugs, such as the opioids.[6–8,27] The absence of daily or monthly variations is consistent with the profile of regular heavy drinking, as are their high levels of alcohol-related disease. Despite this, no case was enrolled in treatment for alcohol dependence at the time of death. These were not young, binge drinkers, and only a single case involved a drinking contest. Indeed, only a single case was aged younger than 25 years. Death typically occurred at home, with spirits most frequently implicated. A significant minority had been drinking denatured alcohol.

While males predominated, as they do in all forms of substances toxicity deaths,[6–8,27] a quarter of cases were female. What stands out from these cases is their similarity to their male counterparts. There were no significant gender differences in their alcohol histories, toxicology or level of disease. While female toxicity cases may be less common than male cases, their clinical profile is identical to that of the more frequently seen male cases.

The mean BAC of 0.420 g/100 ml cases was similar to those previously in other studies, and is a concentration generally considered fatal.[13,12-16] While BACs ranged as high as 0.741 g/100 ml, however, one in five cases had BACs between 0.300 and 0.349 g/100 ml. Lower alcohol concentrations are frequently seen in cases where death is attributed to multiple drug toxicity involving the combined effects of alcohol and other central nervous system depressants.[26] These data indicate that, in the absence of any significant drug interactions, any concentration in excess of 0.300 g/100 ml may be indicative of a toxicity death, even amongst long-term, and presumably highly tolerant, drinkers. The lack of association of BAC with either age or BMI, despite wide ranges in these variables, is consistent with long-standing tolerance.

Of course, we do not know the peak concentration of cases. Back estimation was not possible as there were no witnesses in many cases to estimate the period between the consumption of the final drink and death. The ratios of BACs to both urine and vitreous humour concentrations were, however, similar to those reported previously.[12,13,24,25] Using the >1.25 urine/blood ratio criterion,[13,24,25] the overwhelming majority of cases where both urine and blood analyses were available appeared to have been in the absorptive phase of alcohol metabolism at the time of death.

The health of decedents generally appears to have been very poor. Alcohol-related disease was highly prevalent, as were other forms of systemic disease. Not surprisingly, hepatic disease was almost universal. Cardiac disease was also present in the majority of cases, in all probability reflecting at least in part the long-term cardiotoxic effects of alcohol and the strong association between heavy alcohol consumption and smoking.[28] There is a complex relationship between alcohol consumption and heart disease, with coronary artery atherosclerotic protective effects well described at low levels of consumption, but high levels of alcohol consumption being strongly linked with a range of cardiovascular diseases, including hypertension, coronary atherosclerosis, congestive heart failure and stroke.[29,30] There is also a strong relationship between excessive alcohol consumption and diabetes mellitus,[31] and in relation to this, it should be noted that over half were overweight or obese.

No toxicological testing for nicotine or its metabolite cotinine was reported in these autopsies. We are therefore unable to comment on the effects of smoking on cardiovascular disease in this study group, although we expect that likely there were high rates of smoking in this study population, and smoking can be expected to compound the adverse health effects of excessive alcohol consumption.[28]

While alcohol-related neurologic disease was present in a significant minority, there were no cases of Wernicke's encephalopathy or Korsakoff's syndrome. This is somewhat surprising, given the high prevalence of alcohol-related disease, and may reflect broader changes in epidemiology. Since 1991, there has been mandatory thiamine fortification of Australian bread, and the incidence of these pathologies has declined markedly.[32]

As in all studies caveats need to be considered. Firstly, care should be taken in extrapolating to other alcohol toxicity cases, as we did not have access to national data. The demographic characteristics, however, were typical of studies of alcohol-related death.[11–16] A strength of the current study, however, was that all analyses were conducted by the same laboratory, with full autopsy and police reports available. Secondly, in all studies of this nature, it is possible that some persons dying of alcohol toxicity have been mistakenly issued death certificates giving natural causes of death, and not have been reported to the Coroner.

In summary, the typical alcohol toxicity death was a middle-aged male with a long history of regular, heavy drinking, and significant levels of systemic disease. While less frequent, the clinical profile of female cases was identical to that of males. Even amongst alcohol tolerant individuals with long histories of heavy drinking, death from toxicity may occur at concentrations of 0.300 g/100 ml.

*Ethical approval*

Ethical approval for the study was received from the Sydney Local Area Health District.

*Funding*

None.

*Conflict of interest*

There are no conflicts of interest to declare for Professor Shane Darke, Associate Professor Johan Duflou, Ms Michelle Torok or Ms Tatiana Prolov.

## Acknowledgement

The National Drug and Alcohol Research Centre at the University of NSW is supported by funding from the Australian Government.

## References

1. Heather N, Peters TJ, Stockwell T, editors. *International handbook of alcohol dependence and problems*. Chichester: John Wiley & Sons; 2001.
2. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009;**373**:2223–33.
3. Garriott JC. *Medicolegal aspects of alcohol*. 3rd ed. Tucson: Lawyers & Judges Publishing; 1996.
4. Norstrom T. Per capita alcohol consumption and all-cause mortality in 14 European countries. *Addiction* 2001;**96**(Suppl. 1):S113–28.
5. Norstrom T, Ramstedt M. Mortality and population drinking: a review of the literature. *Drug Alcohol Rev* 2005;**24**:537–47.
6. Below E, Lignitz E. Cases of poisoning in post-mortem examinations at the Institute of Forensic Medicine in Greifswald- analysis of five decades of post-mortems. *Forensic Sci Int* 2003;**133**:125–31.
7. Jones AW, Kugelberg FC, Ahlner HJ. Drug poisoning deaths in Sweden show a predominance of ethanol in mono-intoxications, adverse drug-alcohol interactions and poly-drug use. *Forensic Sci Int* 2011;**206**:43–51.
8. Kivisto JE, Mattila VM, Parkkari J, Kannus P. Incidence of poisoning deaths in Finland, 1971–2005. *Hum Exp Toxicol* 2008;**27**:567573.
9. Yoon YH, Stinson FS, Yi H, Dufour MC. Accidental alcohol poisoning mortality in the United States, 1996–1998. *Alcohol Res Health* 2003;**27**:110–8.
10. Zaridze D, Maximovitch D, Lazarev A, Igitov V, Boroda A, Boreham J, et al. Alcohol poisoning is a main determinant of recent mortality trends in Russia: evidence from a detailed analysis of mortality statistics and autopsies. *Int J Epidemiol* 2009;**38**:143–53.
11. Bellis M, Bolster MA, Doyle CT. The role of alcohol in deaths presenting to the Coroner's Service in Cork City and County. *Ir Med J* 2009;**102**:13–5.
12. Garriott JC, DiMaio JM, Petty CS. Death by poisoning: a ten-year survey of Dallas County. *J Forensic Sci* 1982;**27**:868–79.
13. Jones AW, Holmgren P. Urine/blood ratios of ethanol in deaths attributed to acute alcohol poisoning and chronic alcoholism. *Forensic Sci Int* 2003;**135**:206–12.
14. Nordrum I, Eide TJ, Jørgensen L. Alcohol in a series of medico-legally autopsied deaths in northern Norway 1973–1992. *Forensic Sci Int* 2000;**110**:127–37.
15. Sjogren H, Eriksson A, Ahlm K. Role of alcohol in unnatural deaths: a study of all deaths in Sweden. *Alcohol Clin Exp Res* 2000;**24**:1050–6.
16. Taylor HL, Hudson RP. Acute ethanol poising: a two-year study of deaths in North Carolina. *J Forensic Sci* 1977;**22**:639–53.
17. Jeffries JL, Towbin JA. Dilated cardiomyopathy. *Lancet* 2010;**375**:752–62.
18. Kawano Y. Physio-pathological effects of alcohol on the cardiovascular system: its role in hypertension and cardiovascular disease. *Hypertens Res* 2010;**33**:181–91.
19. Roerecke M, Greenfield TK, Kerr WC, Bondy S, Cohen J, Rehm J. Heavy drinking occasions in relation to ischaemic heart disease mortality: an 11–22 year follow-up of the 1984 and 1995 US National Alcohol Surveys. *Int J Epidemiol* 2011;**40**:1401–10.
20. Ramstedt M. Per capita alcohol consumption and liver cirrhosis mortality in 14 European countries. *Addiction* 2001;**96**(Suppl. 1):S19–33.
21. Berild D, Hasselbalch H. Survival after a blood alcohol of 1127 mg/dL. *Lancet* 1981;**2**:363.
22. Johnson RA, Noll EC, Rodney WM. Survival after serum ethanol concentration of 1.5%. *Lancet* 1982;**2**:1394.
23. Darke S, Duflou J, Torok M, Prolov T. Characteristics, circumstances and toxicology of sudden or unnatural deaths involving very high range alcohol concentrations. *Addiction* 2013;**108**:1411–7.
24. Jones AW. Urine as a biological specimen for forensic analysis of alcohol and variability in the urine-to-blood ratio. *Toxicol Rev* 2006;**25**:15–35.
25. Kugelberg FC, Jones AW. Interpreting results of ethanol analysis in postmortem specimens: a review of the literature. *Forensic Sci Int* 2007;**165**:10–29.
26. IBM Inc. *IBM SPSS Statistics 20.0*. Chicago: SPSS Inc.; 2011.
27. Darke S, Duflou J, Torok M. The comparative toxicology and major organ pathology of fatal methadone and heroin toxicity cases. *Drug Alcohol Depend* 2010;**106**:1–6.
28. Grant B, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States. *Arch Gen Psychiatry* 2004;**61**:1107–15.
29. Roerecke M, Rehm J. Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. *Am J Epidemiol* 2010;**171**:633–44.
30. Roerecke M, Rehm J. The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. *Addiction* 2012;**107**:1246–60.
31. O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health: the razor-sharp double-edged sword. *J Am Coll Cardiol* 2007;**50**:1009–14.
32. Truswell AS. Australian experience with the Wernicke-Korsakoff syndrome. *Addiction* 2000;**95**:829–32.